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cqc

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on June 22, 2005.

David Saliwanchik

David R. Saliwanchik, Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. HB-43
Patent No. 6,852,754

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Amy E. Wright, Ross E. Longley, Srinivasa Reddy Natala, John K. Reed
Issued	:	Feb 8, 2005
Patent No.	:	6,852,754
For	:	Biologically Active Linderazulene Terpenes

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 7, line 16:	Page 11, line 1:
"WV(MeOH)"	--UV(MeOH)--
Column 7, line 18:	Page11, line 2:
"(11270) run;"	--(11270) nm;--.

M:\Linda\DOC\COC\HB43\hb43_certrequest.doc/DNB/lm

Patent Reads:	**Application Reads:**
Column 7, line 26:	Page 11, line 8:
"(12077) run;"	--(12077) nm;--
Column 9, line 12:	Page 13, line 26:
"A summary of results in this assay for compounds I and II can be found in Table 3. Table 3. In vitro activity of compounds I and II against tumor cell lines."	-- A summary of results in this assay for compounds I and II can be found in Table 3. Table 3. In vitro activity of compounds I and II against tumor cell lines. (Please note this sentence should be the heading of Table 3) --
Column 11, line 6:	Page 17, line 13:
"HFABMS"	--HRFABMS--
Column 11, line 51:	Page 18, line 20:
"7.69(t),"	--7.69(s),--

A true and correct copy of pages 11, 13, 17, 18 of the specification as filed, which support Applicants' assertion of errors on the part of the Patent Office, accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: P.O Box 142950
Gainesville, FL 32614-2950

DRS/lm

Attachments: Certificate of Correction;
Copies of pages 11, 13, 17, and 18 of the specification.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,852,754

DATED : February 8, 2005

INVENTORS : Amy E. Wright, Ross E. Longley, Srinivasa Reddy Natala, John K. Reed

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 38, "WV(MeOH)" should read --UV(MeOH)--.

Column 1,
Line 67, "(11270) run;" should read --(11270) nm;--.

Column 3,
Line 66, "(12077) run;" should read --(12077) nm;--.

Column 5,
Line 46, "A summary of results in this assay for compounds I and II can be found in Table 3. Table 3. In vitro activity of compounds I and II against tumor cell lines." should read -- A summary of results in this assay for compounds I and II can be found in Table 3.
Table 3. In vitro activity of compounds I and II against tumor cell lines.--.

Column 5,
Line 48, "HFABMS" should read --HRFABMS--.

Column 5,
Line 52, "7.69(t)," should read --7.69(s),--.

MAILING ADDRESS OF SENDER:

Saliwanchik, Lloyd & Saliwanchik
P.O Box 142950
Gainesville, FL 32614-2950

PATENT NO. 6,852,754
No. of add'l. copies
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FORM PTO-1050 (REV. 3-75) UNITED STATES PATENT AND TRADEMARK OFFICE

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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DATED : February 8, 2005

INVENTORS : Amy E. Wright, Ross E. Longley, Srinivasa Reddy Natala, John K. Reed

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Column 5,
Line 55, "WV(MeOH)" should read --UV(MeOH)--.

Column 5,
Line 58, "(11270) run;" should read --(11270) nm;--.

Column 5,
Line 65, "(12077) run;" should read --(12077) nm;--.

Column 6,
Line 2, "WV(MeOH)" should read --UV(MeOH)--.

Column 6,
Line 11, "(11270) run;" should read --(11270) nm;--.

Column 6,
Line 18, "(12077) run;" should read --(12077) nm;--.

Column 6,
Line 47, "(11270) run;" should read --(11270) nm;--.

Column 6,
Line 58, "(12077) run;" should read --(12077) nm;--.

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PATENT NO. 6,852,754
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11-Carbomethoxylinderazulene (I): amorphous pink solid, mp 138-139 °C; UV (MeOH) λ_{max} (ε) 389 (8282), 376 (6381), 325 (11880), 308 (20367), 247 (10048), 228 (11270) nm; IR (NaCl neat) ν_{max} 2946, 2918, 2853, 1678, 1447, 1408, 1387, 1305, 1217, 1188, 1133, 1079, 1056, 939 cm^{-1}; ^1H and ^{13}C NMR data are given in Table 1. HRFABMS m/z: 255.1033 (calcd for $C_{16}H_{15}O_3$ $[M+H]^+$, 255.1021).

11-Formyllinderazulene (II): amorphous pink solid, mp 136 °C; UV (MeOH) λ_{max} (log ε) 395 (7308), 332 (9385), 316 (13308), 293 (10615), 260 (14284), 215 (12077) nm; IR (NaCl neat) ν_{max} 2956, 2923, 2853, 2746, 1641, 1634, 1398, 1374, 1297, 1286, 1233, 1148, 1081, 1044, 943 cm^{-1}; ^1H and ^{13}C NMR data are given in Table 2; HRFABMS m/z: 225.0917 (calcd for $C_{15}H_{13}O_2$ $[M+H]^+$, 225.0915).

Table 1: NMR Spectral Data for 11-carbomethoxylinderazulene (I) in $CDCl_3$.

Position	^{13}C δ, mult.	^1H δ (mult., *J* in Hz)	HMBC[a]	NOESY
2	141.1 d	7.56 (s)	C-3, C-3a, C-9a	H-10
3	120.3 s			
3a	126.3 s			
4	130.7 d	9.99 (s)	C-3a, C-4a, C-7a, C-9a	H-10
4a	116.4 s			
5	136.3 s			
6	137.0 d	8.24 (d, 3.7)	C-4a, C-5, C-7a	H-7
7	116.1 d	7.28 (d, 3.7)	C-4a, C-5, C-6, C-7a	H-6 H-12
7a	139.3 s			
8	141.1 s			
9	115.7 d	7.69 (s)	C-3a, C-7a, C-8, C-9a, C-12	H-12
9a	159.1 s			
10	8.0 q	2.45 (s, 3H)	C-2, C-3, C-3a	H-4, H-2
11	166.3 s			
12	25.2 q	2.93 (s, 3H)	C-7a, C-8, C-9	H-7, H-9
$-OCH_3$	50.9 q	3.94 (s, 3H)	C-11	

[a] HMBC Correlation from H number to carbon atoms listed

plates, Nunc, Denmark) were established at 1 x 10^5 cells/mL in TCM or TCM containing the test agent at 0.03 - 5.0 μg/mL. After 48-h exposures, P388 cells were enumerated using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) as described in the literature (M.C. Alley, et al., Cancer Res. 48:589, 1988). PANC-1 cells were enumerated in the same manner after 72 hours exposure. The results were expressed as percent inhibition compared to the negative (no drug) control. Positive drug controls of varying dilutions of 5-fluorouracil and adriamycin (Sigma Chemical Co., St Louis, MO) were included to monitor drug sensitivity of the cell line.

To quantitate the effects on cell proliferation and resulting IC_{50} values, 75 mL of warm growth media containing 5 mg/mL MTT is added to each well, cultures returned to the incubator, and left undisturbed for 3 hours. To spectrophotometrically quantitate formation of reduced formazan, plates are centrifuged (500 x g, 10 minutes), culture fluids removed by aspiration, and 200 μl of acidified isopropanol (2 mL concentrated HC1/liter isopropanol) added per well. The absorbance of the resulting solutions is measured in a plate reader (TECAN Spectra SLT; TECAN U.S., Research Triangle Park, NC) at 570 nm and a 650 nm reference filter. The absorbance of test wells is divided by the absorbance of drug-free wells, and the concentration of agent that results in 50% of the absorbance of untreated cultures (IC_{50}) is determined by linear regression of logit-transformed data (D. J. Finney, Statistical Method in Biological Assay, third ed., pp.316-348, Charles Griffin Co., London, 1978). A linear relationship between tumor cell number and formazan production has been routinely observed over the range of cell densities observed in these experiments. The two standard drug controls (indicated above) are included in each assay as a check to monitor the drug sensitivity of each of the cell lines and IC_{50} values are determined for each drug-cell combination.

A summary of results in this assay for compounds I and II can be found in Table 3.

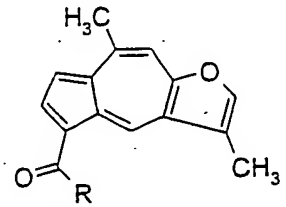
Table 3. In vitro activity of compounds I and II against tumor cell lines.

Heading for Table

6. The compound, according to claim 1, having the following spectroscopic properties: UV (MeOH) λ_{max} (ε) 389 (8282), 376 (6381), 325 (11880), 308 (20367), 247 (10048), 228 (11270) nm; IR (NaCl neat) ν_{max} 2946, 2918, 2853, 1678, 1447, 1408, 1387, 1305, 1217, 1188, 1133, 1079, 1056, 939 cm^{-1}; HRFABMS m/z: 255.1033 (calcd for $C_{16}H_{15}O_3$ $[M+H]^+$, 255.1021); ^{13}C (observed at 125 MHz in $CDCl_3$) δ 166.3 s,; 159.1 s, 141.1 s, 141.1 d,139.3 s, 137.0 d,136.3 s, 130.7 d, 126.3 s, 120.3 s, 116.4 s, 116.1 d, 115.7 d, 50.9 q, 25.2 q, and 8.0 q; ^1H NMR (observed at 500 MHz in $CDCl_3$) δ 2.45 (s, 3H), 2.93 (s, 3H), 3.94 (s, 3H), 7.28 (d, 3.7), 7.56 (s),7.69 (s), 8.24 (d, 3.7), 9.99 (s).

7. The compound, according to claim 1, having the following the following spectroscopic properties: UV (MeOH) λ_{max} (log ε) 395 (7308), 332 (9385), 316 (13308), 293 (10615), 260 (14284), 215 (12077) nm; IR (NaCl neat) ν_{max} 2956, 2923, 2853, 2746, 1641, 1634, 1398, 1374, 1297, 1286, 1233, 1148, 1081, 1044, 943 cm^{-1}; HRFABMS m/z: 225.0917 (calcd for $C_{15}H_{13}O_2$ $[M+H]^+$, 225.0915); ^{13}C (observed at 125 MHz in $CDCl_3$) 187.1 d, 159.4 s, 141.8 d, 141.7 s, 141.5 s, 141.3 d, 135.1 s, 131.5 d, 126.6 s, 120.5 s, 117.6 d, 117.4 s, 117.4 d, 25.2 q, 8.0 q; ^1H NMR (observed at 500 MHz in $CDCl_3$) 10.29 (s), 9.99 (s), 8.09 (d, 3.7), 7.80 (s), 7.56 (s), 7.32 (d, 3.7), 2.94 (s, 3H), 2.46 (s, 3H).

8. A method for inhibiting cellular proliferation, said method comprising administering to a patient in need of such treatment an effective amount of a compound having the following structure:



wherein R is selected from H, OR_1, or NZ_1Z_2;

R_1 is selected from the group consisting of H, C_1 to C_8 alkyl, phenyl, substituted aryl and benzyl; and

Z_1 and Z_2 are the same or different and independently chosen from the group consisting of H, C_1 to C_8 alkyl, phenyl, substituted aryl or wherein NZ_1Z_2 represents an amino acid which is linked to the linderazulene nucleus via the nitrogen to form a peptide bond; or a salt of said compound.

9. The method, according to claim 8, wherein R=OCH_3.

10. The method, according to claim 8, wherein R=H.

11. The method, according to claim 8, wherein the compound is a hydrazone or semicarbazone derivative of 11-formyl linderazulene (I).

12. The method, according to claim 8, wherein said compound has the following spectroscopic properties: UV (MeOH) λ_{max} (ε) 389 (8282), 376 (6381), 325 (11880), 308 (20367), 247 (10048), 228 (11270) nm; IR (NaCl neat) ν_{max} 2946, 2918, 2853, 1678, 1447, 1408, 1387, 1305, 1217, 1188, 1133, 1079, 1056, 939 cm^{-1}; HRFABMS m/z: 255.1033 (calcd for $C_{16}H_{15}O_3$ $[M+H]^+$, 255.1021); ^{13}C (observed at 125 MHz in $CDCl_3$) δ 166.3 s,; 159.1 s, 141.1 s, 141.1 d,139.3 s, 137.0 d,136.3 s, 130.7 d, 126.3 s, 120.3 s, 116.4 s, 116.1 d, 115.7 d, 50.9 q, 25.2 q, and 8.0 q; ^1H NMR (observed at 500 MHz in $CDCl_3$) δ 2.45 (s, 3H), 2.93 (s, 3H), 3.94 (s, 3H), 7.28 (d, 3.7), 7.56 (s), 7.69 (s), 8.24 (d, 3.7), 9.99 (s).

13. The method, according to claim 8, wherein said compound has the following spectroscopic properties: UV (MeOH) λ_{max} (log ε) 395 (7308), 332 (9385), 316 (13308), 293 (10615), 260 (14284), 215 (12077) nm; IR (NaCl neat) ν_{max} 2956, 2923, 2853, 2746, 1641, 1634, 1398, 1374, 1297, 1286, 1233, 1148, 1081, 1044, 943 cm^{-1}; HRFABMS m/z: 225.0917 (calcd for $C_{15}H_{13}O_2$ $[M+H]^+$, 225.0915); ^{13}C (observed at 125 MHz in $CDCl_3$) 187.1 d, 159.4 s, 141.8 d, 141.7 s, 141.5 s, 141.3 d, 135.1 s, 131.5 d, 126.6 s, 120.5 s, 117.6 d, 117.4 s, 117.4 d, 25.2 q, 8.0 q; ^1H NMR (observed at 500 MHz in $CDCl_3$) 10.29 (s), 9.99 (s), 8.09 (d, 3.7), 7.80 (s), 7.56 (s), 7.32 (d, 3.7), 2.94 (s, 3H), 2.46 (s, 3H).

UNITED STATES PATENT AND TRADEMARK OFFICE

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UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

JUN 17 2005

DRS

H1243

PATENT NO.	PATENT DATE
PATENTEE AMY E. wright. Ross etal.	

Paper No.: _____

MAILING DATE

Certificate
JUN 08 2005
of Correction

NOTIFICATION OF RETURN OF PAPERS
RE REQUEST FOR CERTIFICATE OF CORRECTION

The request for a Certificate of Correction in the above-identified patent is returned herewith, together with the PTOL-1050 (SB/44) forms (if submitted), for the reason(s) checked below.

☐ 1. The request is unsigned. The request must be properly signed before it will be considered.

☐ 2. The request does not specifically designate the column and line numbers wherein the errors appear in the patent. A substitute request providing this information is required, for proper consideration.

☐ 3. The FORM PTOL-1050 (SB/44) submitted with your request is not suitable for printing purposes. See the instructions on the blank Form PTO-1050, enclosed.

☒ 4. The Patent No., as shown on papers attach, appears to be incorrect, because:
- ☑ a. The Patent No. on the request and on the PTO-1050 do not agree.
- ☐ b. The name of the patentee on the patented file does not agree with that shown on the enclosed papers..

☐ 5. The record reveals that there is no power of attorney to you in this case. A written power or authorization from the patentee, or assignee, if any, must be submitted, before the request may be considered.

☐ 6. The request cannot be considered, because the paper indicated below was filed on _____, AFTER payment of the issue fee: [See 37 CFR 1.313(B.].
- ☐ a. Amendment purported to be under Rule 312.
- ☐ b. Assignment.
- ☐ c. Priority papers.
- ☐ d. Other (identify) _____.

☐ 7. Other: _____

☐ A. PLEASE RETURN A COPY OF THIS LETTER TOGETHER WITH THE ENCLOSED PAPERS AS CORREECTED TO ENSURE EXPEDIENT ASSOCIATION WITH THE FILE

☐ B. Enclosed are copies of PTOL-1050 for use in typing the subject matter to be printed on the Certificate. This will avoid delay in handling request (See 862 O.G.2).

Decisions and Certificate of Correction Branch

FORM PTOL-396 (8/75)